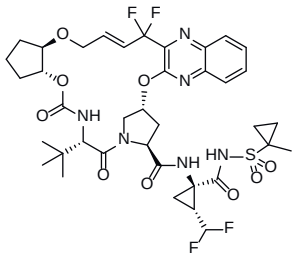
MACROCYCLES

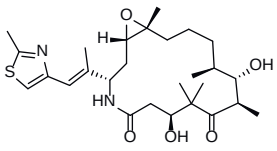
Macrocyclic motifs are commonly found in natural products and also interesting for Drug Discovery especially in efforts to tackle “difficult” targets with extended binding sites. The size and complexity of macrocyclic compounds make possible to ensure numerous and spatially distributed binding interactions, thereby increasing both binding affinity and selectivity. Macrocylic structure often provides necessary balance between degree of structural preorganisation (that may reduce the entropy cost of receptor binding as compared to linear analogues) and sufficient flexibility (comparing to common rigid (poly)cyclic cores) that can facilitate interactions with diverse dynamic protein targets. In addition often macrocycles have favorable ADME- and PK-properties. In spite of such attractiveness for medicinal chemistry the chemical space of macrocycles is still poorly investigated.

Features of Macrocycles

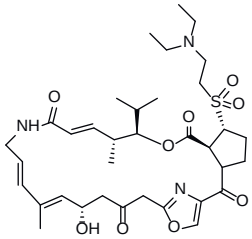
- **Possibility to go beyond "Ro5"**
- **"Friendly" ADME and PK**
- **Complexity / 3D-shape**
- **Novelty**
- **Balance between conformational confinement and flexibility**



Glecaprevir
Abbvie, anti-HCV



Ixabepilone
BMS, chemotherapy

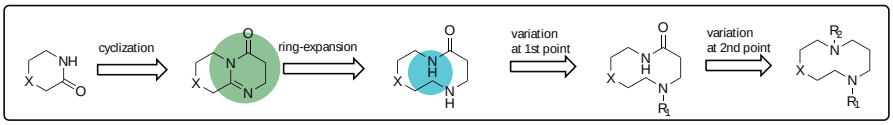


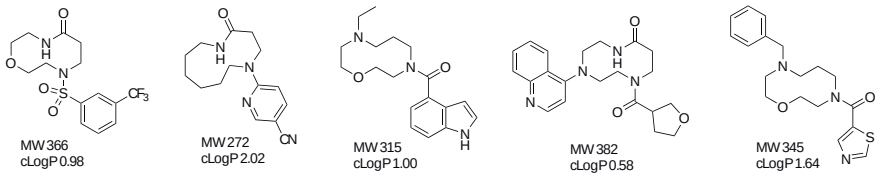
Dalfopristin
Sanofi, antibiotic

Enamine's offer

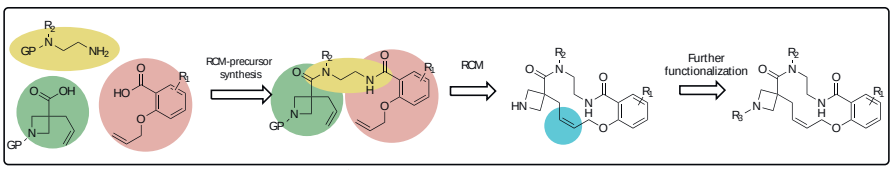
- **Libraries of drug-like compounds with medium sized and macrocyclic cores**
- **MedChem-friendly compounds** *(pass common MedChem filters including PAINS)*
- **Validated macrocyclization chemistry** *(RCM, click, ring-expansion, macrolacton/lactamization, etc.)*
- **Validated scaffolds** *(>10 key intermediates available in 1-5 g)*
- **Decoration with diverse Enamine building blocks (150,000 in stock)**
- **Rapid library synthesis** *(3 weeks for parallel synthesis of up to 200 cmpds from available scaffold)*

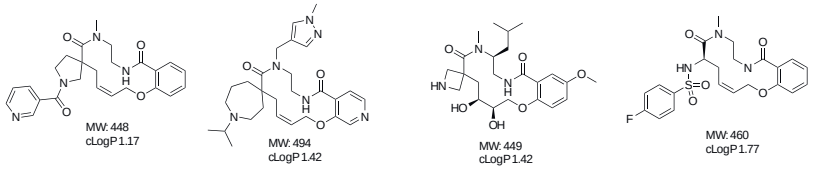
Ring-expansion to build a 10-membered diamino scaffold





Ring Closing Metathesis (RCM) in synthesis of new macrocyclic scaffolds at Enamine





References

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[2] D. Sun *et al. Molecules.* **2013**, 18.
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[4] E. Marsault *J. Med. Chem.*, **2011**, 1961